EZH2 and Endometrial Cancer Development

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Contributor: Qinglei Li

Enhancer of zeste homolog 2 (EZH2), a core component of polycomb repressive complex 2, plays an important role in cancer development. As both oncogenic and tumor suppressive functions of EZH2 have been documented in the literature, the objective of this study is to determine the impact of Ezh2 deletion on the development and progression of endometrial cancer induced by inactivation of phosphatase and tensin homolog (PTEN), a tumor suppressor gene frequently dysregulated in endometrial cancer patients.

Ezh2 endometrial cancer Pten

1. Introduction

Endometrial cancer is the most common cancer in the genital tract in women, with approximately 65,570 new cases and 12,940 deaths each year in the United States [1]. Endometrial cancer is classified into two distinct types [2]. The type I cancer represents the major type (~90%) and is often companied by endometrial hyperplasia [2][3]. The type II cancer accounts for ~10% of the total cases and is more aggressive than the type I cancer [2][3][4][5]. Histologically, the type I cancer is endometrioid carcinoma while the type II cancer consists of several subtypes, including serous carcinoma and clear-cell carcinoma [6]. Notably, the type I, but not the type II, endometrial cancer is related to estrogen stimulation [7]. Using molecular sequencing technologies, endometrial cancer has been classified into the following types by The Cancer Genome Atlas (TCGA) Research Network: DNA polymerase epsilon catalytic subunit (*POLE*) (ultramutated), microsatellite-instability (MSI) (hypermutated), copy-number low, as well as copy-number high [8]. To facilitate the classification in clinical practice, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) has been developed and validated, with the inclusion of immunohistochemical analysis of DNA mismatch repair (MMR) protein and tumor protein p53 (TP53) [9][10][11]. Interestingly, a report shows that a combination of tumor-infiltrating lymphocytes pattern and MMR may be used as a surrogate for the *POLE* mutation group [12]. ProMisE has been used in molecular diagnosis of human endometrial cancer [13].

Significant challenges remain for endometrial cancer treatment. Determining the histological subtype of endometrial cancer is an effective strategy that guides cancer treatment, with an emerging need to incorporate more molecular details into clinical interventions [14]. While surgery remains to be the most common option to treat this gynecological malignancy, new therapeutic strategies targeting actionable mutations and/or molecular pathways are potentially valuable [15][16]. Of particular importance, knowledge gaps need to be filled in areas of early cancer diagnostics, cancer risk stratification, and molecular identity-based treatment options [14].

Phosphatase and tensin homolog (*PTEN*), a tumor suppressor gene, is frequently dysregulated in the type I endometrial cancer patients [2]. Loss of heterozygosity of chromosome 10q where *PTEN* is located (chromosome 10q23.3) or intragenic mutation of *PTEN* has been identified in endometrial cancer [2][17][18][19]. Conditional deletion of *Pten* in the mouse uterus promotes endometrial cancer development, lending credence to the role of PTEN in the pathogenesis of endometrial cancer [20]. Dysregulation of the phosphatidylinositol 3-kinase (PI3K) pathway, mitogen-activated protein kinase (MAPK) pathway, catenin beta 1 (CTNNB1), or AT-rich interaction domain 1A (ARID1A or BAF250) appears common in endometrial cancer patients [21]. Meanwhile, mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*), KRAS proto-oncogene, GTPase (*KRAS*), fibroblast growth factor receptor 2 (*FGFR2*), protein phosphatase 2 scaffold subunit Aalpha (*PPP2R1A*), and tumor protein p53 (*TP53*) have also been identified in endometrioid carcinoma and serous endometrial cancer [21].

Enhancer of zeste homolog 2 (EZH2) is a core component of polycomb repressive complex 2 (PRC2) [22]. EZH2 is a well-established histone methyltransferase that regulates gene expression via inducing the tri-methylation of lysine 27 on histone H3 (H3K27) [23]. EZH2 is overexpressed in both human endometrial cancer cell lines and endometrial cancer tissues [24]. Moreover, gain-of-function [25][26] or loss-of-function [27][28] mutations of EZH2 frequently occur in cancers [23][29]. Of note, both tumor-promoting and tumor-suppressive effects of EZH2 have been documented in cancer development [29]. However, the role of EZH2 in endometrial cancer remains poorly defined.

2. EZH2 in Endometrial Cancer

Both *PTEN* and *EZH2* play important roles in endometrial cancer. The mutation of *PTEN* gene has been identified in ~20% of human endometrial hyperplasia, suggesting its importance in early cancer development [30]. The frequency of *PTEN* mutation appears to be associated with the histotypes of endometrial cancer, as *PTEN* mutation occurs in ~40% of endometrioid cancers but only 5% of serous or clear cell endometrial cancers [19]. EZH2 is overexpressed in endometrial cancer, and its downregulation in endometrial cancer cells inhibits cell proliferation [24][31]. A study has identified a correlation between overexpression of EZH2 in endometrial cancer patients and disease-free and overall survival [32]. This report has further demonstrated that silencing *EZH2* in endometrial cancer cells impairs the expression of growth-related genes such as peroxiredoxin 6 (*PRDX6*) [32]. The mechanisms underlying EZH2 action in endometrial cancer progression remain incompletely understood. However, it appears that microRNA-361/Twist axis plays an important role in mediating the role of EZH2 in driving endometrial cancer development [33]. The evidence points to the therapeutic potential of targeting EZH2. However, EZH2 may also function as a tumor suppressor in myeloma and pancreatic tumor [34][35]. It has been shown that loss of EZH2 in the mouse uterus enhances epithelial cell proliferation [36][37][38] and induces epithelial stratification [39]. Herein, it is found that conditional deletion of both *Ezh2* and *Pten* reduced cell proliferation and uterine growth during early carcinogenesis but exacerbated intraluminal neutrophil accumulation and chronic inflammation during tumor progression, leading to an unfavorable disease outcome. Current results revealed dual roles of EZH2 in the development of endometrial cancer lacking *Pten*, a gene frequently mutated in endometrioid carcinomas.

The uterine weights of *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice were lower than those of *Pten*$^{d/d}$ mice at three weeks of age, accompanied by reduced cell proliferation revealed by Ki67-staining. As EZH2 inhibits uterine epithelial cell proliferation and uterine growth [39][36][37][38], the results suggest that EZH2 plays distinct roles in normal uterine epithelial cells versus malignant epithelial cells. Supporting the assumption that the role of EZH2 in PTEN-depleted epithelial cells differs from that in PTEN-expressing epithelial cells, it was reported that loss of PTEN or activation of AKT switches the tumor suppressive role of EZH2 to an oncogenic function

Neutrophils are the first-line defenders that actively participate in host defense, tissue damage, and inflammatory disease [42]. Tumor-associated neutrophils play important roles in tumor microenvironment, where N1 neutrophils are anti-tumorigenic and N2 neutrophils are pro-tumorigenic [43][44]. The pro-tumorigenic action of neutrophils is generally associated with their effects on cancer cell invasion, extracellular matrix remodeling, and angiogenesis [44]. Although the oncogenic role of EZH2 has been documented, some in vivo experiments suggest a tumor-suppressive function of EZH2. One study showed that loss of EZH2 promotes KRas^{G12D}-driven oncogenesis in pancreatic cancer [35]. In another report, deletion of *Ezh2* accelerates Kras-driven lung adenocarcinoma in a mouse model [45]. In both cases, EZH2 appears to play a role in controlling inflammatory microenvironment [35][45]. It is found that tumor burden was reduced in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice during early tumor development, revealing an oncogenic role of EZH2 in endometrial cancer development. However, unfavorable cancer outcomes were observed in these mice compared with *Pten*$^{d/d}$ mice. The latter effect is likely non-cell autonomous, as dysregulation of EZH2 in cancer cells is known to alter immune response [46]. Indeed, massive accumulation of intraluminal neutrophils is a hallmark of the endometrial cancer in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice at nine weeks of age. The finding is also consistent with a previous report that increased levels of intratumoral neutrophils correlate with a poor cancer outcome [47].

The underlying mechanisms that promote the heightened inflammation in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice remain unclear. However, several important contributing factors were identified by the present study. First, it is found reduced hypoxia in the uteri of *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice at 1 month of age. Elegant studies have demonstrated that hypoxia increases neutrophil recruitment in endometrial cancer induced by PTEN depletion, which serves to restrain the development of endometrial cancer by debridement of the malignant cells [48][49]. Interestingly, reduction of hypoxia causes attenuated neutrophil infiltration. However, these neutrophils gain more efficient capability of attacking cancer cells [49]. Loss of EZH2 limited the extent of hypoxia in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice, likely enhancing the tumoricidal effect of neutrophils [49]. Intraluminal accumulation of cancer cells/debris would in turn stimulate neutrophil influx and cause heightened immune reactions, forming a vicious cycle and resulting in chronic inflammation and/or eliciting secondary infectious event. The exact reasons of how EZH2 ablation led to reduced hypoxia is unclear. However, increased vascularization in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ uteri (Fang X and Li Q, unpublished observation) may be one of the reasons. Second, conditional deletion of *Ezh2* potentiated epithelial stratification in *Pten*$^{d/d}$ mice. The uterus contains simple columnar epithelial cells expressing KRT8 but not KRT14 and p63 [50]. Current results showed that stratified epithelial markers KRT14 and ΔNp63 were expressed earlier in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ uteri than *Pten*$^{d/d}$ uteri, consistent with the previous finding that loss of EZH2 in the uterus promotes the development of basal cells and stratified epithelia [39]. The intensified epithelial stratification in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ uteri

likely reflected the additive effect of loss of EZH2 and PTEN. Uterine epithelial stratification is a pathological event that alters the polarity and function of epithelial cells [51][52]. It is possible that epithelial stratification adversely impacts the progression of endometrial cancer due to altered epithelial cell properties. The role of epithelial stratification in endometrial cancer development in the model requires further investigation. Finally, it was found that epithelia adjacent to the uterine lumen had reduced expression of PGR in *Pten*$^{d/d}$*; Ezh2*$^{d/d}$ mice at one month of age, when epithelial stratification intensified and marked accumulation of intraluminal neutrophils occurred. PGR loss has been associated with increased cell proliferation and metastasis [53][54]. PGR signaling antagonizes estrogen signaling during tumor development [55]. Estrogen is known to promote neutrophil recruitment during mammary involution or breast cancer development [56][57]. Thus, it is tempting to speculate that the reduction of PGR expression is associated with estrogen-directed neutrophil infiltration and heightened inflammation, which merits further investigation.

Endometrial cancer in *Pten*$^{d/d}$ mice is not metastatic to other organs even at 25–36 weeks of age [20][58][59]. However, dysregulation of several key regulators/signaling pathways may trigger metastasis. It have shown that conditional deletion of transforming growth factor β type 1 receptor (*Tgfbr1*) in *Pten*$^{d/d}$ mice promotes pulmonary metastases [58]. Lung metastasis was also reported in a mouse model where PTEN-ablated and K-ras expressed endometrial cancer cells were grafted [60]. In addition, conditional deletion of both *Pten* and dicer 1, ribonuclease type III (*Dicer1*) in the mouse uterus triggers adnexal metastasis [61]. EZH2 expression has been linked to endometrial cancer cell invasion and metastasis [31]. As mice conditionally overexpressing EZH2 are available [62], future investigations are needed to determine whether conditional overexpression of EZH2 in PTEN-depleted uteri impacts metastasis.

From a systems biology perspective, the functions of cells are achieved and coordinated by numerous genes/pathways within a highly interactive network [63]. Cancer may develop when perturbations of protein-protein interactions occur due to gene mutations [64]. Studies on protein-protein interaction networks in cancer may benefit cancer treatment by gaining a holistic view of mechanisms governing tumor development and discovering novel cancer drivers as well as therapeutic targets [65][66]. Studies have begun to explore protein-protein interaction networks in female reproductive cancers including endometrial cancer using an integrative computational approach [67]. Defining the interactome of endometrial cancer remains to be one of the key goals in the future.

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